# Content Uniformity –
# Alternative Statistical Approaches

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# Outline

1. Comments on FDA content uniformity standard

2. Alternative approaches

## FDA Content Uniformity Standards (in part)
## Metered Dose Inhalers and Nasal Sprays

| | |
|---|---|
| Unit | 1 dose per container (10 or 30 canisters) |
| 1st Tier (10 units) Acceptance If: | |
| 0 or 1 outside: | 80%-120% of LC |
| None outside: | 75%-125% of LC |
| 2nd Tier (20 additional units; 30 total) Acceptance If: | |
| 0 or 3 outside: | 80%-120% of LC |
| None outside: | 75%-125% of LC |
| Additional | Mean within 85%-115% of LC |

LC = Labeled Claim

## Comments from a Statistical Perspective

1. FDA tests 10 –30 *containers; in contrast, the* USP tests *doses within 1-3 containers*

   ⇒ FDA, but not USP, addresses batch characteristics

2. Criterion is in the form of a statistical hypothesis test, but is incomplete – no hypotheses!

   (same is true of USP, CPMP, JP, and PhRMA)

3. First tier is an "interim analysis"

## Some Definitions

**False positive rate** (consumer risk, type I error rate, or alpha) -- probability that an "unacceptable" batch passes

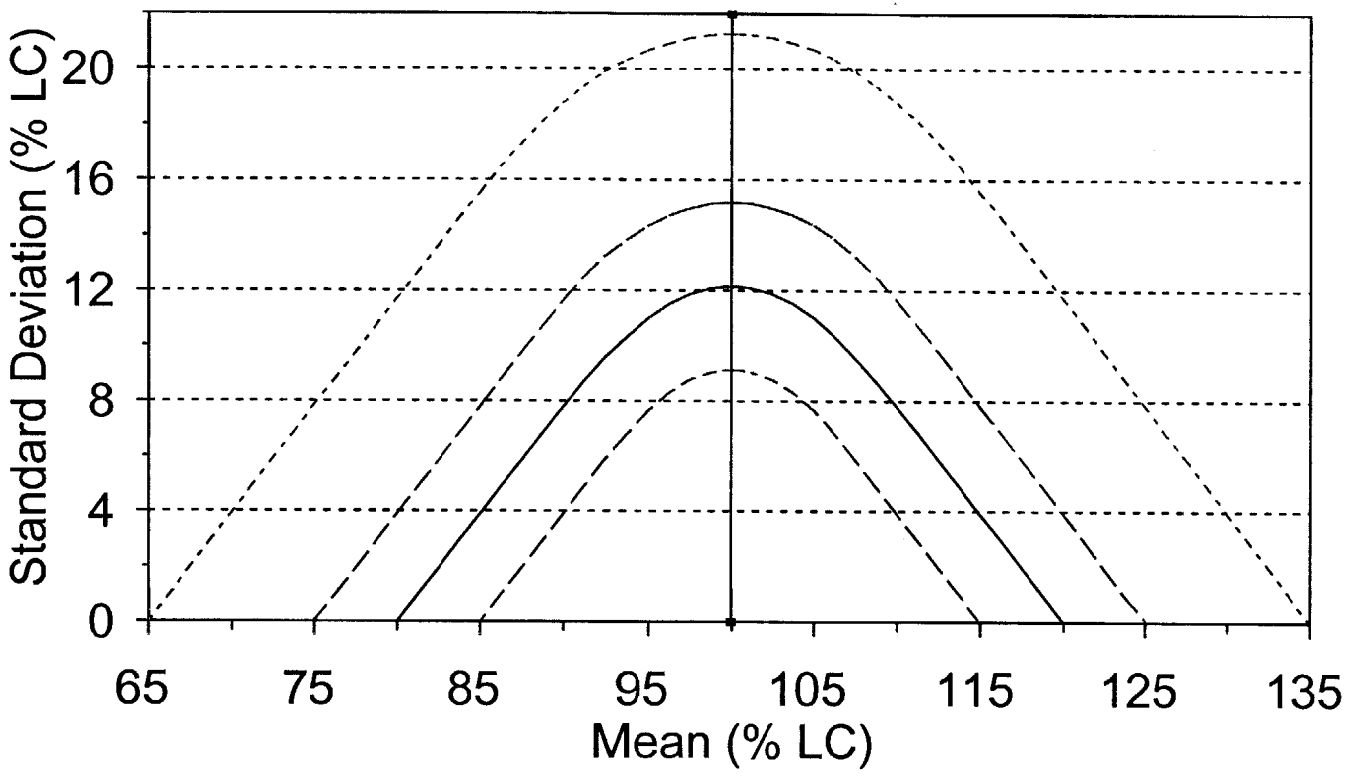
**False negative rate** (producer risk, type II error rate, or beta) -- probability that a good batch does not pass

**Target interval** -- Interval in which most of batch should fall

e.g., 80%/120% of LC for FDA

**Target coverage probability** -- Proportion of batch that should fall within target interval

# Means and Standard Deviations Corresponding to Target Intervals with 90% Coverage



## A Statistician's Alternative Approach -- General

1. Regulatory agency specifies maximum allowed false positive rate (alpha), minimum coverage probability, and target interval

   e.g., "Demonstrate with an alpha of no more than 5% that at least 90% of the batch falls within 80%/120% of LC"

2. Sponsor determines sample size and number of tiers to attain desired level of possible false negative rate ("producer risk")

3. If more than one tier, possible false positive rate determined for all tiers together (using interim analysis methods)

## Statistical Structure of FDA Content Uniformity Standards

1. Test for attributes;

   i.e., uses only whether or not in target interval, not the actual value

2. Hybrid of a two-stage (two-tier) binomial test combined with a "safety net" for very large deviations from LC

   (same for USP and CPMP)

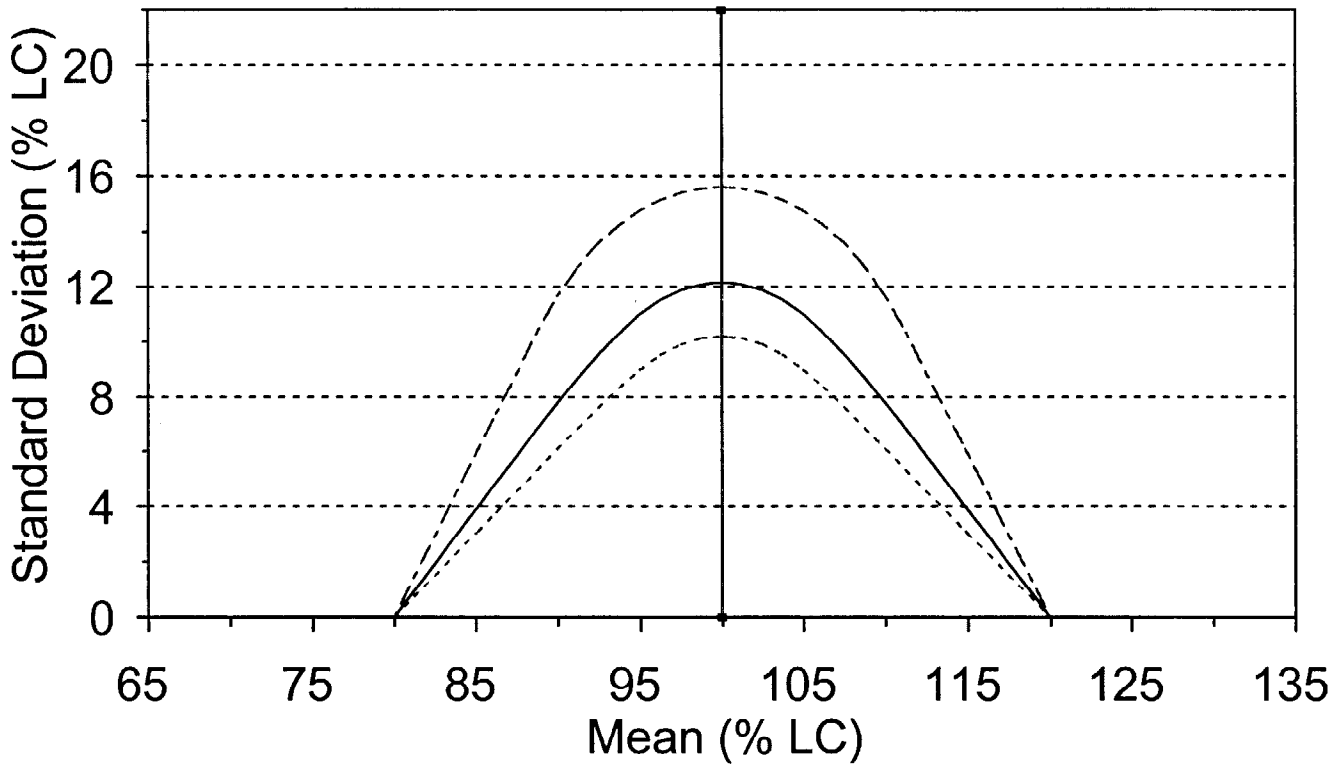
## Some Two-Tier Designs that Control False Positive Rate

These designs have 5% alpha and **10% producer risk**

| Target Coverage Probability | Actual % Inside Target Interval | First Tier | | Second Tier | |
|---|---|---|---|---|---|
| | | $N_1$ | Max. Outside to Accept | $N_1+N_2$ | Max. Outside to Accept |
| 80 | 95 | 23 | 1 | 51 | 4 |
| 90 | 95 | | | >110 | |
| 90 | 98 | 33 | 0 | 84 | 3 |
| 95 | 98 | | | >110 | |
| 60 | 91 | 10 | 1 | 22 | 3 |

Note: Designs based on optimal designs of Simon (*Controlled Clinical Trials*, 1989) that minimize the expected sample size; no "safety net"

# Means and Standard Deviations Corresponding to 80%/120% Target Intervals




Coverage Probability: 80% 90% 95%

## Another Alternative – Test by Value

Tolerance intervals: Data-derived intervals for which can make statements like:

> We are 95% confident that this interval (i.e., the tolerance interval) covers 90% of the population (batch).

The regulatory agency could specify the two percentages (confidence and coverage) and a target interval as a means of setting a quality standard. An acceptable batch would be one whose tolerance interval was contained in the target interval.
(JP and PhRMA proposals)

Note: Tolerance intervals are NOT the same as confidence intervals

# Test by Value, cont.

Two forms of tolerance intervals:

nonparametric (test by attributes)

parametric (normal distribution) (test by value)

(Weissberg and Beatty, *Technometrics*, 1960)

If normal distribution is sufficiently reasonable, parametric tolerance intervals seem likely to make better use of data

i.e., smaller sample size requirements

## Summary Points

**Recommendation:** Regulatory agencies fully specify their criteria, not the acceptance rules

Pluses

- Regulatory agency concentrates on specification of what is acceptable
- Company has more control over design and producer risk

Minuses

- Current standards are so loose, that statistical specification may mean tighter standards (and thus larger sample sizes)